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Biologic Drugs in Pediatric Rheumatology

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ESS performed a literature review and wrote the article. AVR made significant contributions to discussion of content and review/editing of the article prior to submission. All authors read and approved the final manuscript.

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Editorial

The past decade has seen growing use of biologic drugs for the treatment of pediatric rheumatic diseases.¹ The widest range of such treatments are used for juvenile idiopathic arthritis (JIA), although biologics are sometimes given in more refractory cases of juvenile systemic lupus erythematosus (JSLE), juvenile dermatomyositis (JDM) and vasculitis. In this issue of the *Journal*, Al-Mayouf *et al.* report their use of biologic agents in children with rheumatic diseases at a tertiary hospital in Saudi Arabia between January 2001 and December 2011.² A total of 134 patients were treated during this period, 70.1% with JIA, 12.7% with JSLE and 4.5% with vasculitis. As expected for a cohort of predominantly JIA patients, the most frequently-used biologic drugs were those targeting tumour necrosis factor (anti-TNFs), including etanercept, adalimumab and infliximab. The authors have described the use of biologics in various categories of JIA including polyarticular, psoriatic, “familial”, “ankylosing” and “IBD associated arthritis”.

Most of the initial evidence for use of biologics derived from randomised controlled trials (RCTs) including patients with polyarticular JIA.¹ In recent years, studies have been undertaken to investigate the use of these drugs in other categories of JIA including extended oligoarticular (eoJIA), psoriatic (PsJIA) and enthesitis-related arthritis (ERA). A two-phase, randomised placebo-controlled withdrawal study of etanercept was undertaken in 41 patients with active ERA who had intolerance or inadequate response to initial standard treatment.³ In phase I, all patients received open-label etanercept 0.8mg/kg body weight weekly for 24 weeks and the primary end point was at least 30% improvement in ACR Pedi criteria (ACR Pedi 30). This was achieved

in 38 patients (93%) who were then randomised in Phase II either to continue etanercept or placebo for a further 24 weeks. The primary outcome of disease flare occurred in 9 patients on placebo and 3 on etanercept (odds ratio 6.0, $p=0.02$). The study represented 35.6 patient-years (PY) exposure to etanercept with an adverse event (AE) rate of 4.5 per year, most frequently upper respiratory tract infections (URTIs), adverse drug reactions and gastrointestinal infections.

The efficacy and safety of etanercept has also been reported in ERA, eoJIA and PsJIA in an open-label study with a total of 122 subjects.⁴ At week 12 of treatment, achievement of JIA ACR Pedi 30 was 83.3%, 89.7% and 93.1% and of inactive disease was 16.7%, 11.9% and 6.9% in ERA, eoJIA and PsJIA respectively. After long term follow-up at 96 weeks, achievement of JIA ACR Pedi 30 was 78.9%, 88.3% and 82.8% and of inactive disease was 21.1%, 33.3% and 24.1% in ERA, eoJIA and PsJIA respectively.⁵ Overall there were 139.5 AEs / 100 PY, most commonly infections, headache, pyrexia and diarrhoea. There were no malignancies, active tuberculosis (TB), demyelinating diseases or death reported

Forty-seven patients in the study of Al-Mayouf *et al.* were given adalimumab, mostly with polyarticular and systemic categories of JIA. A double-blind, placebo-controlled RCT has now provided evidence of efficacy of adalimumab in ERA.⁶ Forty-six patients, age 6-18 years with active ERA, were randomised (31 to adalimumab at 24mg/m² every other week, 15 to placebo) for 12 weeks, with open-label treatment with adalimumab up to 192 weeks. The primary efficacy endpoint was percentage change in active joint count between baseline and week 12: -62.6% in the adalimumab group versus -11.6% in the placebo group ($p=0.039$). At 52 weeks in the open-label phase, 84.8% achieved ACR Pedi 30 and 60.9% ACR Pedi 90 responses. The most frequent

AEs were URTIs, injection site pain and increased alanine aminotransferase (ALT). Taking all these studies together, there is now evidence of efficacy of etanercept and adalimumab across a range of JIA categories with a similar AE profile as reported in other long term studies and no new safety signals.

Uveitis associated with JIA is an important disease which is amenable to biologic treatment in cases of methotrexate intolerance or resistance.⁷ Al-Mayouf *et al.* reported only a single patient with uveitis, who was treated with etanercept, although it is not clear whether some of the patients given biologics for JIA had eye disease in addition to arthritis. Current guidelines do not recommend etanercept as treatment for JIA-associated uveitis and the greatest evidence supports adalimumab as the first biologic drug.⁸ A double-blind, placebo-controlled RCT of adalimumab was stopped early due to efficacy after randomising 90 patients.⁹ Initial analysis of the primary endpoint ("time to treatment failure") showed a positive effect in favour of adalimumab with a hazard ratio of 0.27 (95% confidence interval 0.13-0.52, $p < 0.0001$). AEs were seen in a similar proportion of patients in the treatment and placebo groups. An open-label study of subcutaneous tocilizumab for anti-TNF-refractory JIA-associated uveitis is now underway.¹⁰

Systemic JIA (sJIA), which has a distinct immunobiology and is considered by many an autoinflammatory rather than autoimmune disease, was reported in 42 patients in the cohort of Al-Mayouf *et al.* Most received anti-TNF treatment at some stage and many appear to have received at least two different biologic agents (including anakinra in 31% and tocilizumab in 21%). The diverse range of biologic treatments used likely reflects the lack of a strong evidence base for management of sJIA during the reporting

period. Since the end point of this study in 2011, there has been a significant shift in the management of sJIA on the basis of evidence from RCTs of biologics targeting interleukin (IL)-1 (anakinra and canakinumab) and IL-6 (tocilizumab).¹ A systematic review and meta-analysis of RCTs of anakinra, canakinumab, rilonacept and tocilizumab for treatment of sJIA has recently been published.¹¹ This reported that all biologic agents had shown efficacy statistically significantly superior to placebo. Canakinumab and tocilizumab were more effective than rilonacept, however heterogeneity between the studies' designs limited the quality of the evidence base for this comparison. In terms of serious adverse events (SAEs), there were no differences between any of the four biologics and placebo.

Importantly when discussing biologic drugs, which have a comparatively short history of use in childhood rheumatic diseases, Al-Mayouf *et al.* have reported AEs. The 134 children received a total of 273 different biologic treatments and experienced 95 AEs, most frequently infusion- or injection-related reactions and infections in 18, 14 and 23 patients respectively. Although different types of AEs are detailed for individual biologics, there are no data on the cumulative drug exposure time or rates of AE per patient-year therefore comparison directly with other studies is not possible. The data are presented attributing AEs to each biologic treatment, however since each drug was used for a range of different diseases there is potential for confounding by the underlying diagnosis.

The safety of biologics in children with rheumatic diseases has been a focus of several long-term extension studies and national registries published recently. In a study from Finland including 348 patients (total 1516 PY) receiving biologics for JIA or associated uveitis, the overall rate of AEs was 191/100 PY, most commonly mild

infections, injection site or infusion reactions and increase in ALT.¹² The rate of SAEs / 100 PY was 11.4 on etanercept, 11.8 on infliximab, 10.1 on adalimumab, 15.7 on abatacept, 31.2 on tocilizumab and 87.5 on rituximab. The median follow-up was 51 months and no malignancies or TB were diagnosed. Due to their immunosuppressive effects, infections are an ongoing concern in children receiving biologic agents. By combining data from clinical trials, extension studies and registries, Horneff calculated the rate of serious infections per 100 PY: 1.28 on etanercept, 3.42 on infliximab, 1.42 on adalimumab, 3.03 on golimumab, 1.33 on abatacept and 8.62 on tocilizumab.¹³

Compared with JIA, there is a substantially smaller evidence-based for use of biologics in other pediatric rheumatic diseases, often based on case series or uncontrolled studies. One exception is the randomised withdrawal trial of canakinumab for treatment of cryopyrin-associated periodic syndrome (CAPS), which includes chronic infantile neurological, cutaneous and articular (CINCA) syndrome and Muckle-Wells syndrome (MWS).¹⁴ In the initial open-label treatment phase, 34 (97%) of 35 patients had a complete response within 8 weeks after the first injection of canakinumab. This treatment would not have been available to Al-Mayouf *et al.* However, their use of anakinra, which also targets the IL-1 pathway, in all 5 patients with CAPS is supported by several observational studies.¹⁵

The most frequent use of a biologic drug, other than for JIA, in the cohort of patients from Saudi Arabia was rituximab for JSLE. Evidence for its use mainly derives from controlled adult studies and case series in children.¹ A recent retrospective study using the UK JSLE Cohort identified 63 patients who received 104 courses of rituximab with the most common indication being lupus nephritis.¹⁶ There were statistically

significant improvements in biomarkers of disease activity and the dose of oral corticosteroids.

Biologic drugs have already effected significant improvements in disease control in JIA, JIA-associated uveitis and CAPS. On the horizon are more convenient routes of administration and drugs targeting novel biological pathways. Currently trials are underway to investigate subcutaneous administration of tocilizumab and abatacept which have previously been shown to be efficacious when given intravenously for JIA.¹ Tofacitinib, a Janus kinase inhibitor which can be administered orally, is undergoing investigation in patients with polyarticular-course JIA. Patients 5-17 years old with active SLE are being recruited into an RCT of belimumab, a fully humanised monoclonal antibody against soluble B-lymphocyte stimulator (BLyS). Alongside trials of novel biologic drugs, long-term extension studies and registries will be essential to monitor for adverse events, particularly in children who have their whole lives ahead of them.

References

1. Sen ES, Ramanan AV. New age of biological therapies in paediatric rheumatology. *Arch Dis Child*. 2014;99(7):679-85.
2. Al-Mayouf SM, Alenazi A, AlJasser H. Biologic agents therapy for Saudi children with rheumatic diseases: indications and safety. *Int J Rheum Dis*. 2014.
3. Horneff G, Foeldvari I, Minden K, Trauzeddel R, Kummerle-Deschner JB, Tenbrock K, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. *Arthritis Rheumatol*. 2015;67(8):2240-9.
4. Horneff G, Burgos-Vargas R, Constantin T, Foeldvari I, Vojinovic J, Chasnyk VG, et al. Efficacy and safety of open-label etanercept on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: part 1 (week 12) of the CLIPPER study. *Ann Rheum Dis*. 2014;73(6):1114-22.
5. Constantin T, Foeldvari I, Vojinovic J, Horneff G, Burgos-Vargas R, Nikishina I, et al. Two-year Efficacy and Safety of Etanercept in Pediatric Patients with Extended Oligoarthritis, Enthesitis-related Arthritis, or Psoriatic Arthritis. *J Rheumatol*. 2016;43(4):816-24.
6. Burgos-Vargas R, Tse SM, Horneff G, Pangan AL, Kalabic J, Goss S, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. *Arthritis care & research*. 2015;67(11):1503-12.
7. Sen ES, Dick AD, Ramanan AV. Uveitis associated with juvenile idiopathic arthritis. *Nat Rev Rheumatol*. 2015;11(6):338-48.
8. Bou R, Adan A, Borrás F, Bravo B, Calvo I, De Inocencio J, et al. Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. *Rheumatol Int*. 2015;35(5):777-85.
9. Ramanan AV, Dick AD, McKay A, Jones A, Williamson P, Compeyrot-Lacassagne S, et al. A Randomised Controlled Trial of the Clinical Effectiveness, Safety and Cost-Effectiveness of Adalimumab in Combination with Methotrexate for the Treatment of Juvenile Idiopathic Arthritis Associated Uveitis [abstract]. *Arthritis Rheumatol*. 2015;67(Suppl 10):3931-3.
10. A phase II trial of tocilizumab in anti TNF refractory patients with JIA associated uveitis (APTITUDE study) [Internet]. BioMed Central. 2015 [cited 22 DEC 2015]. Available from: <http://www.isrctn.com/ISRCTN95363507>.
11. Tarp S, Amarilyo G, Foeldvari I, Christensen R, Woo JM, Cohen N, et al. Efficacy and safety of biological agents for systemic juvenile idiopathic arthritis: a systematic review and meta-analysis of randomized trials. *Rheumatology*. 2016;55(4):669-79.
12. Tarkiainen M, Tynjala P, Vahasalo P, Lahdenne P. Occurrence of adverse events in patients with JIA receiving biologic agents: long-term follow-up in a real-life setting. *Rheumatology*. 2015;54(7):1170-6.
13. Horneff G. Biologic-associated infections in pediatric rheumatology. *Current rheumatology reports*. 2015;17(11):66.
14. Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, Leslie KS, Hachulla E, Quartier P, et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. *N Engl J Med*. 2009;360(23):2416-25.

15. ter Haar NM, Oswald M, Jeyaratnam J, Anton J, Barron KS, Brogan PA, et al. Recommendations for the management of autoinflammatory diseases. *Ann Rheum Dis*. 2015;74(9):1636-44.
16. Watson L, Beresford MW, Maynes C, Pilkington C, Marks SD, Glackin Y, et al. The indications, efficacy and adverse events of rituximab in a large cohort of patients with juvenile-onset SLE. *Lupus*. 2015;24(1):10-7.